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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,408	PARIKH ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-27* is/are pending in the application.

4a) Of the above claim(s) *12-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 12-27 are pending. Claims 18-27 are under consideration in the instant office action.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on January 9, 2005 is acknowledged. The traversal is on the ground(s) that the differences between the groups are insufficient to require a separate search or place an undue burden upon the Examiner. This is not found persuasive because as shown in the previous office action Groups I and II are classified in class 600, subclass 532 and class 700, subclass 702, respectively. The methods of Groups I and II, although sharing some commonality are different. Claims 12-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 9, 2006.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The objection to the abstract **is withdrawn**, because Applicant's amendment to the abstract has corrected the minor informality, which prompted the objection. The objection to the specification due to the improper use of Trademarks **is withdrawn**, because it appears that all trademarks used in the specification have been capitalized.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

The rejection of claims 1-11 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps **is withdrawn**, because said claims have been cancelled.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claims 1-10 under 35 U.S.C. 103(a) as being unpatentable over Kharitonov et al. (*Monaldi Arch. Chest Dis.*, 1996, *51(6)*, pp 533-537) **is withdrawn**, because said claims have been cancelled.

The rejection of claims 1-11 under 35 U.S.C. 103(a) as being unpatentable over Kharitonov et al. (*Monaldi Arch. Chest Dis.*, 1996, *51(6)*, pp 533-537) in view of Information for Transcriptionists (MedicalNotes.com), http://web.archive.org/web/20010410235147/http://www.medicalnotes.com/TranscriptionInfo.htm /> **is withdrawn**, because said claims have been cancelled.

The rejection of claims 1-10 under 35 U.S.C. 103(a) as being unpatentable over Silkoff et al. (U.S. Patent No. 6,010,459) **is withdrawn**, because said claims have been cancelled.

The rejection of claims 1-10 under 35 U.S.C. 103(a) as being unpatentable over Gaston et al. (U.S. patent No. 6,033,368) in view of Kharitonov et al. (*The Lancet* 1994, *343*, pp 133-135) **is withdrawn**, because said claims have been cancelled.

Claims 18-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moilanen et al. (US 2002/0193698) in view of Kharitonov et al. (*Monaldi Arch. Chest Dis.*, "Nitric Oxide in Exhaled Air is a New Marker of Airway Inflammation," 1996, *51(6)*, pp 533-537; IDS).

Moilanen teaches **a method for measuring nitric oxide concentration in exhaled air** through a blow tube of measuring equipment. The method is used to diagnose an inflammatory lung disease in a patient whereby **an increased nitric oxide concentration indicates an inflammatory lung disease,** such as alveolitis (abstract).

Moilanen teaches that exhaled nitric oxide (eNO) concentration is higher than normal in subjects suffering from inflammatory lung diseases (e.g. asthma and alveolitis). The increased concentration of eNO is attributed to inflammation in the lungs, and can therefor be used as an indicator of inflammatory disease [0002]. The [eNO] can be measured by an analyzer intended for that purpose. In known measuring methods, a person exhales into an analyzer such that the flow rate of the exhaled air remains substantially constant. By this measuring method it is possible to detect a rise in the nitric oxide concentration of the exhaled air and thus to conclude,

on the basis of the increased nitric oxide concentration, that there is inflammation in the lungs [0003].

Moilanen teaches in Figures 2 and 3 graphs of exhaled NO concentration ([eNO]) in units of ppb versus exhalation rate in units of ml/s for healthy patients (Figs. 2-3) and patients with asthma (Figs. 2-3) and alveolitis (Fig. 2). It is clear from the graph of Fig. 2 that a healthy patient with **an exhalation rate of approximately 50 ml/s** has **an [eNO] of about 20 ppb**, whereas those suffering from inflammatory diseases have higher [eNO]s. The bronchial NO flux of patients with asthma is higher than that of the healthy persons or the patients with alveolitis because of bronchial inflammation. The patients with alveolitis suffering from alveolar inflammation have, in turn, higher alveolar NO concentration than healthy persons or asthmatics [0026]. Figure 3 is specific to the [eNO] of children who are considered "healthy" and those diagnosed with asthma [0027]. A healthy child has an [eNO] of approximately **10 ppb** at an **exhalation rate of approximately 50 ml/s**, whereas an asthmatic child has an eNO of approximately 50 ppb at the same exhalation rate. Because very low exhalation flow rates have been used in the measurements of Fig. 2, it is possible to calculate the nitric oxide concentration of the bronchial wall tissue and the NO diffusion capacity in said tissue. On the basis of these calculated variables, **it is possible to draw conclusions on the intensity and location of the inflammation in the lungs** in the same manner as in the material of FIG. 2 [0027].

Moilanen teaches the results of studies conducted prior to the publication of US 2002/0193698 [0029]-[0030], wherein **patients with asthma** undergoing an 8 week treatment of inhaled glucocorticoids exhibited a significant decrease in bronchial NO flux **after one week of treatment** and "normal" NO flux **after 8 weeks of treatment** compared to healthy controls (i.e.

a baseline). Moilanen states that the results of their previous studies "support the role of present invention in differential diagnosis of alveolar and bronchial inflammatory diseases. The results also suggest that **the present method can be used to follow-up drug treatment of inflammatory lung diseases and provide means to assess the efficacy of such treatment** [0031]."

Moilanen lacks the express teaching of modifying active dosages used in treatment, changing the active agent, and subsequently evaluating the effects of these treatment protocol changes.

Kharitonov teaches that it is known in the art that **exhaled nitric oxide** (NO) is increased in patients with inflammatory diseases of the airways, such as **asthma** and bronchiectasis and **may be modulated by inhaled corticosteroids** (p 533, right hand column, 2nd paragraph, 2nd sentence). Corticosteroids are known medicaments.

Kharitonov suggest that exhaled NO may provide a noninvasive means of monitoring inflammation in the respiratory tract (p 533, right hand column, 3rd paragraph, 1st sentence).

Kharitonov teaches that it is suggested in the art that in inflammatory diseases increases in exhaled NO are due to induction of a third isoform of the NO synthase enzyme (iNOS). It is known in the art that glucocorticoids inhibit the induction of iNOS in epithelial cells *in vitro* and *in vivo*, and **reduce exhaled NO levels in asthmatic patients to normal** (p 534, right hand column, 2nd paragraph, 1st and last sentences and left hand column, 1st paragraph, 1st line).

Kharitonov teaches that regarding asthma, there is now persuasive evidence **that levels of NO are increased in association with airway inflammation and are decreased with anti-**

inflammatory therapy (p 535, 1st paragraph, 1st sentence in the section entitled "Clinical Relevance of Exhaled NO" with the sub-heading "Asthma").

Kharitonov teaches that a double-blind study of **inhaled budesonide**, a synthetic anti-inflammatory corticosteroid, **showed a progressive reduction of exhaled NO down to normal values after three weeks of therapy** (p 535, left hand column, 2nd paragraph, 4th sentence in the section entitled "Effects of Therapy").

Kharitonov summarizes the state of the prior art by stating that the advantage of exhaled NO is that the measurement is completely non-invasive and **can be performed repeatedly**. In addition, because the measurement is not specific, absolute values are less important than serial measurements in individual patients. For example, the value of this approach in asthmatic patients has been shown **where the dose of the inhaled steroid is changed**, resulting in **increased levels of NO when the dose is reduced and lower levels of NO when the dose is increased**. Reduction of eNO levels is observed in anti-inflammatory treatment and may be used in **monitoring whether therapy is adequate** and **to ascertain the therapeutic effectiveness of new antiasthma drugs** (e.g. selective phosphodiesterase inhibitors, leukotriene antagonists and synthesis inhibitors, and immunomodulators). Because the measurement of eNO is precise and reproducible, it **may facilitate dose-response effects** with anti-inflammatory treatments (p 537, right hand column, "Summary" section).

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Moilanen and Kharitonov, because both references teach the utility of monitoring exhaled nitric oxide levels as a metric to evaluate anti-inflammatory treatment. A skilled artisan would have been motivated to combine the teachings

of Moilanen and Kharitonov, because both references describe similar methods and Moilanen provides data comparing the exhaled nitric oxide profiles of healthy patients, asthmatics, and patients suffering from alveolitis, as a function of the flow rate of exhaled air. It would have been apparent to a skilled artisan that one would use the curve for exhaled nitric oxide (NO) of healthy patients provided by Moilanen as a baseline to ascertain the effectiveness of treatment because the achievement of normative exhaled nitric oxide levels is obviously a goal of these therapeutic methods. It would have been apparent that a skilled artisan would use a patient's initial eNO measurements as a baseline for comparison to ascertain whether treatment was effective.

Although the prior art references do not expressly discuss the use of "trends," it is obvious from Kharitonov's teaching of studies of budesonide treatment of asthmatics that the phrase "progressive reduction of exhaled NO" implies an observed trend, the use of said observation, and the artisan's practice of making multiple measurements over a period of time – three weeks in the study referred to by Kharitonov. A skilled artisan aware of the teachings of Kharitonov would understand that changing the dosage of active agent used would be expected to affect the observed eNO levels and said artisan would be motivated to adjust the dosage amount appropriately to improve a patient's response to treatment. It would also have been apparent to a skilled artisan that changing the active agent used could result in increased or reduced NO levels, requiring monitoring to ascertain the effect of the new therapeutic drug, and subsequent appropriate adjustment of the therapy frequency and dosage, because Kharitonov stated that eNO measurement "may facilitate the measurement of dose-response effects with anti-inflammatory treatments." Therefore, due to the aforementioned reasoning, a skilled artisan

would have had a reasonable expectation of success upon combination of the prior art references and claims 18-27 are *prima facie* obvious over the teachings of the prior art.

Claims 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hampton et al. (US 2003/0073919) in view of Moilanen et al. (US 2002/0193698).

Hampton teaches **techniques for identifying and guiding treatment for medical conditions**, based upon the carbon dioxide concentration in the patient's breath. The techniques of the invention may further be used **to monitor the effectiveness of the treatment** (abstract). The method taught by Hampton is directed to techniques for rapidly and reliably distinguishing **obstructive lung disease** from restrictive lung disease. In addition, the invention is directed to techniques for monitoring the response of the patient to treatment for the condition [0010]. The term "obstructive lung disease" encompasses asthma, which is a disease associated with inflammation of the lungs.

Hampton's method may take into consideration, for example, the duration of a steady rise of the concentration of carbon dioxide in the breath or the rate of increase of the concentration of carbon dioxide, as measured by the initial angle and slope of the capnogram. The method may also **compare the carbon dioxide concentration in the breath with a characteristic curve**. The method **may further include monitoring the condition of the patient following treatment** [0013]. The method may also be used to guide treatment, **including determining the presence of lung conditions, determining the severity of the conditions, and selecting medicaments to treat the conditions** [0015]. For example, system 70 helps to determine the nature of the condition and further helps guide treatment of the patient. Processor 82 may report

the severity of the condition, **suggest a medicine for the condition**, **recommend that the measurements be repeated**, or that the patient be instructed to breathe in a particular manner. In some circumstances, such as **the treatment of some forms of asthma**, proper treatment produces a prompt improvement in the condition of the patient and **this improvement can be monitored.** The invention need not be embodied in a method that analyzes only carbon dioxide concentration in the breath, but may include other diagnostic measurements such as measurements of heart rate, respiration rate, blood pressure, electrocardiogram, and blood oxygenation [0052]-[0055].

Hampton lacks the teaching of the measurement of exhaled nitric oxide.

The teachings of Moilanen have been set forth above.

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Hampton and Moilanen, because both carbon dioxide and nitric oxide are gases present in exhaled air that have been measured as a means to monitor a medical condition (e.g. asthma) and the treatment of said condition. A skilled artisan would have been further motivated to combine the teachings Hampton and Moilanen, because Moilanen provides data useful in establishing the "normative levels" of exhaled NO and Hampton's method facilitates the use of a processor (i.e. computer) to analyze clinical data and suggest means of changing (i.e. guiding) a patient's treatment. Because both prior art references teach methods of monitoring respiratory conditions by the measurement of the concentration of exhaled gases -either carbon dioxide or nitric oxide- and Moilanen's teaching provide data useful in establishing a baseline of "normal levels" of exhaled nitric oxide, a skilled artisan would have

had a reasonable expectation of success upon combination. It would have been apparent to a skilled artisan that Hampton's teaching of comparing the concentration of carbon dioxide in breath to a characteristic curve could be modified to compare a patient's exhaled nitric oxide measurements to characteristic curves (i.e. baselines) to evaluate treatment efficacy. Using Hampton's teachings, in which the processor reports the condition's severity and recommends medications, a person of ordinary skill in the art at the time of the instant invention would have obviously been able to ascertain whether the appropriate step in treatment required a change in medication and or dosage frequency. Likewise, given the severity of the condition, the skilled artisan would be capable of determining the required frequency of [eNO] measurement to properly evaluate treatment progress.

Response to Arguments

Applicant's arguments with respect to claims 1-11 have been considered but are moot in view of the new ground(s) of rejection. It is also noted that original claims 1-11 have been cancelled.

Conclusion

Claims 18-27 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo, Ph.D.
Examiner

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER